REMARKS

Claims 1-2, and 4-63 are pending. Claims 6, 7, 10-23, 26-29, 32, 33, 36, 41, 42, and 44-63 are cancelled without prejudice. Claims 1, 2, 4, 5, 8-10, 24, 25, 30, 31, 34-40, and 43 are rejected. Claims 1, 30, and 34 are amended.

Applicant respectfully requests reconsideration because the amendments and arguments are believed to put the application in complete condition for allowance. However, applicant respectfully questions the propriety of making the Action final, as further analyzed.

CLAIM REJECTIONS UNDER 35 U.S.C. §102

Claims 1-2, 4-5, 8-10, 24-25, 30-31, 34-40 are rejected under 35 U.S.C. §102(b) as anticipated by SU Patent 1685448 and U.S. Patent No. 6,030,612. Applicant respectfully disagrees.

Applicant reiterates his position regarding the finality of the Office Action. The previous Office Action had not specifically "asserted" anticipatory teachings, as applicant explained. Therefore, in preparing and filing his Response, applicant had no way of knowing if he was addressing the Examiner's basis of the rejection. The Examiner's post-submission acknowledgement that applicant was correct does not, however, relieve the Examiner from her requirement to show the particular part of the reference relied upon. The Examiner's characterization of the particular part of the reference as "clear and unmistakable" lends further credence to applicant's position that it would have been a simple matter to point out such portions.

With respect to the Soviet patent, Applicant respectfully reasserts his argument that the enzyme is the sole active ingredient, evidenced in numerous ways in numerous portions of the application such as:

Title: Selective Enzyme Treatment of Skin Conditions

Field of the Invention: enzymes that selectively target one or more layers of skin

Summary of the Invention: ...using a composition containing at least one enzyme that affects one or more particular layers of skin. (page 4, lines 5-8)

Detailed Description (page 8, lines 4-10):

> The invention is directed to compositions and methods to selectively treat, alleviate, or prevent conditions in mammals that affect one or more layers of skin. For example, the compositions are chosen and formulated to selectively remove part or all of an epidermal layer of skin, and/or part or all of a dermal layer of skin. The compositions contain one or more enzymes from the oxidoreductase, transferase, lyase, isomerase, ligase, and hydrolase classes of enzymes to remove affected skin layers.

"The concentration of the enzyme, or mixture of enzymes, in the composition is in the range of ...." (page 15, lines 19-21)

"Any type of suitable, physiologically acceptable enzyme formulation may be used, as is known to one of skill in the art." (page 18, lines 1-2)

The section to which the examiner cites makes clear that the enzyme is the component effecting the claimed result (page 18, lines 14-18):

> The composition containing an enzyme or mixture of enzymes may also contain other compounds that have desirable therapeutic, cosmetic. and/or aesthetic

> properties, that either do not affect or only minimally affect the activity of the enzyme. These so-called co-additives may be used in any of the formulations that contain the enzyme.

The text that follows this discloses teaching penetrants, moisturizers, chelators, and exfoliants (page 18, line 18 to page 19, line 12).

In contrast, the SU patent discloses, along with an enzyme and DMSO, theophylline. Theophylline is known as a drug (see attached pages from Goodman and Gilman, The Pharmacologic Basis of Therapeutics, Gilman et al. Eds., Eighth Edition, Pergamon Press, 1990, pages 619-620, "The Methylxanthines Chemistry." "Caffeine, theophylline, and theobromine are methylated xanthines". "Theophylline, caffeine, and theobromine share in common several pharmacological actions of therapeutic interest", and at page 623:

> Three basic cellular actions of the methylxanthines have received major attention in studies to explain their diverse effects. Listed in order of their increasing sensitivity to methylxanthines, they are (1) those associated with translocations of intracellular calcium, (2) those mediated by increasing accumulation of cyclic nucleotides, and (3) those mediated by blockage of receptors for adenosine.

The SU patent does not distinguish efficacy among the three components in its composition. In addition, applicant has demonstrated that one skilled in the art considers theophylline as a drug. The SU patent discloses its composition contains 17-23% theophylline. Applicant has demonstrated that one skilled in the art would know that addition of theophylline would be expected to affect at least translocation of intracellular calcium, increasing accumulation of

cyclic nucleotides, and adenosine receptor associated properties. Applicant therefore respectfully asserts that he has met his burden to show that theophylline as a drug would materially affect the basic and novel characteristics of the claimed invention at least because of its effect on the above-described calcium translocation, cyclic nucleotides, and receptive blocking properties processes. Thus, the "consisting essentially of" limitation would exclude theophylline.

With respect to the '612 patent, the present claims require "at least one hydrolase selective for a layer of skin" (claim 1), or a protease in an amount to selectively remove at least one epidermal layer containing a skin condition (independent claim 24), or at least one hydrolase at a concentration selective for regulating depth of skin treatment (independent claim 34).

The '612 patent does not disclose a method where a hydrolase is selective for a layer of skin. The '612 patent specifically states that the multifunctional enzyme has at least one of a chymotrypsin, trypsin, elastase, collagenase or exo peptidase activity (column 1, lines 45-58). As applicant has disclosed, these enzymes are Class 3.4 hydrolases (page 13, lines 18-20). While the '612 patent defines "hydrolase" as not limited to proteases such as trypsin and chymotrypsin (column 7, line 65 to column 8, line 3), the '612 patent requires the multifunctional enzymes have at least one of these activities ("The enzyme has at least one of a chymotrypsin, trypsin, elastase, collagenase or exo peptidase activity, and a molecular weight between about 20 kd and about 40 kd." (column 1, lines 55-58). Thus, the '612 patent does not disclose a method

using a composition without such activity, and thus does not disclose a method using a composition with applicant's class 3.1, 3.2, and 3.3 hydrolases. It is not a proper anticipation reference because it does not disclose each and every limitation expressly or inherently in that single prior art reference. For example, applicant's hydrolase may act on non-peptide bonds, such that it would not have any of the activities of the '612 patent.

Further, the Examiner states "The term 'selective' is used in the phrase "selective for a layer of skin" and modifies the phrase "at least one hydrolase" (page 6 instant Office Action). However, the '612 patent does not disclose that its multifunctional enzyme is "selective for a layer of skin", as applicant requires. Applicant has amended claims 1, 30 and 34 to clarify this selectivity.

Still further, the '612 patent is directed only to antimicrobial uses (title: antimicrobial uses of multifunctional enzyme"). Hence, the '612 patent is disclosed for numerous organs/tissues that are diseased due to a microbial component; examples are teeth, intestines, tumors, blood vessels, anus, etc. (column 2, lines 38-64). In contrast, applicant's method does not require a specific etiology of the condition affecting at least one layer of skin in order for the patient to be treated.

For at least these reasons, applicant respectfully asserts his claims are not anticipated by the '612 patent.

CLAIM REJECTIONS UNDER 35 U.S.C. §103

Claims 1, 2, 4, 5, 8-10, 24, 25, 30, 31, and 34-40 are rejected under 35 U.S.C. §102(e) as anticipated by, or in the alternative, under 35 U.S.C. §103(a) as obvious over the Freeman published application.

Applicant has amended claims 1, 30, and 34 to require topical or injectable administration as supported at least on page 8, lines 15-17, and Examples 1-13.

For the reasons above, Applicant respectfully asserts that Freeman is not obvious and requests that the rejection be withdrawn.

CONCLUSION

Applicant does not believe that there is any fee due with this submission. However, if any fees are necessary the Commissioner may consider this to be a request for such and charge any required fees to Deposit Account 23-3000.

The Examiner is invited to contact applicant's undersigned representative with any issues or questions.

Respectfully submitted,
WOOD, HERRON & EVANS. L.L.P.

Beverly A. Lyman

Beverly A. Lyman, Ph.D.
Reg. No. 41,961

2700 Carew Tower
441 Vine Street
Cincinnati, OH 45202
(513) 241-2324
(513) 421-7269 facsimile

GOODMAN and GILMAN's

The Pharmacological Basis of Therapeutics

EIGHTH EDITION

PERGAMON PRESS
Member of Maxwell Macmillan Pergamon Publishing Corporation
New York • Oxford • Beijing • Frankfurt • São Paulo • Sydney • Tokyo • Toronto

Press Offices:

Pergamon Press, Inc., Maxwell House, Fairview Park,
Elmsford, New York 10523, U.S.A.

Pergamon Press plc, Headington Hill Hall,
Oxford OX3 0BW, England

REPUBLIC Pergamon Press, 0909 China World Tower, No. 1 Jian Guo
Men Wai Avenue, Beijing 100004, Peoples's Republic of China

REPUBLIC ANY Pergamon Press GmbH, Hammerweg 6,
D-6242 Kronberg, Federal Republic of Germany

Pergamon Editora Ltda, Rua Eça de Queiros, 346,
CEP 04011, Paraiso, São Paulo, Brazil

IA Pergamon Press Australia Pty Ltd., P.O. Box 544,
Potts Point, NSW 2011, Australia

Pergamon Press, 8th Floor, Matsuoka Central Building,
1-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160, Japan

Pergamon Press Canada Ltd., Suite 271, 253 College Street,
Toronto, Ontario M5T 1R5, Canada

Library of Congress Cataloging-in-Publication Data

Goodman and Gilman's the pharmacological basis of
therapeutics.

Includes bibliographical references.
Includes index.
1. Pharmacology. 2. Chemotherapy. I. Goodman,
Louis Sanford, 1906- II. Gilman, Alfred, 1908-
III. Gilman, Alfred Goodman, 1941-
IV. Title: Pharmacological basis of therapeutics.
[DNLM: 1. Drug Therapy. 2. Pharmacology. QV 4 G6532]
RM300.G644 1991 615'.7 90-7660
ISBN 0-08-040296-8 (hardcover)

Printing: 2 3 4 5 6 7 8 9 10 Year: 0 1 2 3 4 5 6 7 8 9

Printed in the United States of America

In this textbook, reference to proprietary names of drugs is ordinarily made only in chapter sections dealing with preparations. Such names are given in SMALL-CAP TYPE, usually immediately following the official or nonproprietary titles. Proprietary names of drugs also appear in the index.

The paper used in this publication meets the minimum requirements of American National Standard for Information Sciences—Permanence of Paper for Printed Library Materials, ANSI Z39.48-1984

PREFACE

THIS eighth edition
tics marks its fiftieth
of the accelerating pa
the twentieth century.
sance of the teaching
chapters on the chem
covered sulfonamides
pharmacology; to list
modern biology on pl
DNA technology, det
major progress towar
from appreciation of
macokinetics. Despit
writing of this book t
the First Edition, whi
widespread and succ
pharmacology, and o

While those famili
the organization of th
in addition to extens
expanded and now in
important sections on
this section reflects t
ergic receptors that
those on drugs that
matopharmacology
therapy of inflamma
agents; antifungal ag
newly marketed dru
important examples
(tissue plasminogen
drug entries.

Most of the con
current understan
ganization of the
book. The
Two new
Taylor.

In addition
production
assistan
Ferguson
was ex
Gilman
comp
Gi
prio

as a barrier, metabolic derangements occur, including loss of a postulated epithelium-derived relaxing factor with properties similar to those of the endothelium-derived relaxing factor in blood vessels (*see* Chapter 5).

As appreciation of the complexity of the pathophysiology of asthma has increased, certainty as to the mechanism of action and cellular targets of therapeutic agents has decreased. For example, there is controversy as to whether theophylline produces bronchodilatation primarily by causing direct relaxation of bronchial smooth muscle or whether indirect effects, such as reduction of the release and action of spasmogens, are more important. Moreover, the ability of the methylxanthines to block adenosine receptors has focused attention on the potential role of adenosine in asthma. On the positive side, these uncertainties have unleashed a host of investigations into the nature and role of various chemical mediators, and they have encouraged the development of specific inhibitors of the formation and action of thromboxane and the leukotrienes, as well as antagonists for PAF and adenosine. These and related issues have been reviewed in several recent symposia (Symposium, 1986a, 1987a, 1988a, 1988b, 1988c).

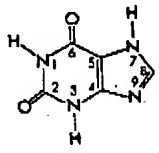
THE METHYLXANTHINES

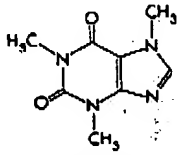
Source and History. Theophylline, caffeine, and theobromine are three closely related alkaloids that occur in plants widely distributed geographically. It is believed that paleolithic man discovered the principal caffeine-containing plants throughout the world and made beverages from them. At least half the population of the world consumes tea (containing caffeine and small amounts of theophylline and theobromine), prepared from the leaves of *Thea sinensis*, a bush native to southern China and now extensively cultivated in other countries. Cocoa and chocolate, from the seeds of *Theobroma cacao*, contain theobromine and some caffeine. Coffee, the most important source of caffeine in the American diet, is extracted from the fruit of *Caffea arabica* and related species. Cola-flavored drinks usually contain considerable amounts of caffeine, in part because of their content of extracts of the nuts of *Cola acuminata* (the guru nuts chewed by the natives of the Sudan) and in part because of the addition of caffeine as such in their production (*see* Graham, 1978).

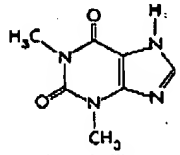
The basis for the popularity of all the caffeine-containing beverages has been the ancient belief that these beverages had stimulant and antisoporific actions that elevated mood, decreased fatigue, and increased capacity for work. For example, legend credits the discovery of coffee to a prior of an Arabian convent. Shepherds reported that goats that had eaten the berries of the coffee plant gamboled and frisked about all through the night instead of sleeping. The prior, mindful of the long nights of prayer that he had to endure, instructed the shepherds to pick the berries so that he might make a beverage from them.

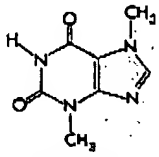
Classical pharmacological studies, principally of caffeine, during the first half of this century confirmed these experiences and revealed that methylxanthines possess other important pharmacological properties as well. These properties were exploited for a number of years in a variety of therapeutic applications; many of these have now been replaced by more effective agents. However, in recent years there has been a resurgence of interest in the therapeutic use of the natural methylxanthines and synthetic derivatives thereof, principally as a result of increased knowledge of their cellular basis of action and their pharmacokinetic properties.

Chemistry. Caffeine, theophylline, and theobromine are methylated xanthines. Xanthine itself is dioxypurine and is structurally related to uric acid. Caffeine is 1,3,7-trimethylxanthine; theophylline, 1,3-dimethylxanthine; and theobromine, 3,7-dimethylxanthine. The structural formulas of xanthine and the three naturally occurring xanthine derivatives are as follows:


Xanthine


Caffeine


Theophylline


Theobromine

The solubility of the methylxanthines is low and is much enhanced by the formation of complexes (usually 1:1) with a wide variety of compounds. The most notable of such complexes is that between theophylline and ethylenediamine (to form *aminophylline*). The formation of complex double salts (*e.g.*, caffeine and sodium benzoate) or true salts (*e.g.*, *choline theophyllinate [oxtriphylline]*) also enhances aqueous solubility. These salts or complexes dissociate to yield the parent methylxanthines when dissolved in aqueous solution and should not be confused with covalently modified derivatives such as *dyphylline* (1,3-dimethyl-7-(2,3-dihydroxypropyl)-xanthine).

A large number of derivatives of the methylxanthines have been prepared and examined for their ability to inhibit cyclic nucleotide phosphodiesterases and to antagonize receptor-mediated actions of adenosine (the two best-characterized cellular actions of the methylxanthines). In general, both activities are reduced in derivatives that lack substituents at position 1 or contain substituents at position 7, as compared with the corresponding dialkylxanthine (*see* Persson, in Symposium, 1985). For example, the order of po-

tency for the naturally occurring methylxanthines is theophylline > caffeine > theobromine. Congeners of theophylline with larger nonpolar substituents at positions 1 and 3 usually display enhancement of both activities (Choi *et al.*, 1988). Addition of aromatic, cyclohexyl, or cyclopentyl groups at position 8 usually increases affinity for adenosine receptors markedly but reduces inhibition of cyclic nucleotide phosphodiesterases (Martinson *et al.*, 1987). Although neither caffeine nor theophylline discriminates between the subtypes of adenosine receptors (*see* below), certain derivatives of 1,3-dipropyl-8-phenylxanthine display marked selectivity for A_1 receptors, while some analogs of caffeine display appreciable selectivity for A_2 receptors (*see* Daly *et al.*, and Bruns *et al.*, in Symposium, 1987b). In addition, certain nonxanthine compounds, notably the triazoloquinazolines, are potent antagonists at adenosine receptors (*see* Williams and Jarvis, in Symposium, 1988d).

PHARMACOLOGICAL PROPERTIES

Theophylline, caffeine, and theobromine share in common several pharmacological actions of therapeutic interest. They relax smooth muscle, notably bronchial muscle, stimulate the central nervous system (CNS), stimulate cardiac muscle, and act on the kidney to produce diuresis. Since theobromine displays a low potency in these pharmacological actions, it has all but disappeared from the therapeutic scene.

Smooth Muscle. The methylxanthines relax various smooth muscles. The most important action in this respect is their ability to relax the smooth muscles of the bronchi, especially if the bronchi have been constricted either experimentally by a spasmogen or clinically in asthma. Theophylline is the most effective of the xanthines and produces a definite increase in vital capacity. It is, therefore, of value in the treatment of bronchial asthma.

The mechanisms underlying theophylline-induced bronchodilatation *in vitro*, much less those operating *in vivo*, are not at all clear. In general, the concentrations of methylxanthines that produce bronchodilatation *in vivo* are considerably lower than those required to relax various preparations of airway muscle studied *in vitro*. For example, concentrations of theophylline greater than 50 μM are required to relax bronchiolar segments from human lung previously contracted by carbachol (Finney *et al.*, 1985); this corresponds to the concentration of free drug attained at the top of the therapeutic range (20 μg/ml). One prominent explanation of the effect *in vitro* is based on the ability of methylxanthines to inhibit cyclic nucleotide phosphodiesterases and on the association between increased accumulation of adenosine 3',5'-monophosphate (cyclic AMP) or of guanosine 3',5'-monophosphate (cyclic GMP) and the relaxation of smooth muscle. Supporting evidence for this idea includes the correlation between the potency of various xanthine derivatives to induce relaxation and to inhibit the hydrolysis of cyclic AMP, as well as their ability to potentiate relaxation induced by β_2-adrenergic agonists, which is thought to be mediated by cyclic AMP (*see* Symposium, 1985). However, such correlations are not evident *in vivo*, and numerous investigations in man have failed to indicate that combinations of theophylline and β_2-adrenergic agonists produce synergistic therapeutic responses (*see* Handslip *et al.*, 1981). Although there is evidence that release of catecholamines participates in theophylline-induced bronchodilatation in short-term animal studies, it is unlikely that such a mechanism operates during the long-term treatment of human asthma (*see* Persson, in Symposium, 1985). The potential role of blockade of adenosine receptors in theophylline-induced bronchodilatation *in vivo* will be discussed in a later section.

Central Nervous System. Theophylline and caffeine are potent stimulants of the CNS; theobromine is virtually inactive in this respect. Traditionally, caffeine has been considered the most potent of the methylxanthines; however, theophylline produces more profound and potentially more dangerous CNS stimulation than does caffeine.

Persons ingesting caffeine or caffeine-containing beverages usually experience less drowsiness, less fatigue, and a more rapid and clearer flow of thought. Comparable salutary effects of low doses of theophylline have not been investigated. As the dose of caffeine or theophylline is increased, signs of progressive CNS stimulation are produced, including nervousness or anxiety, restlessness, insomnia, tremor

Secretion. Methylxanthines augment release of the secretory products of a number of endocrine and exocrine tissues. One exception to this general statement is the ability of methylxanthines to inhibit secretion by mast cells and possibly other sources of mediators of inflammation. A number of the therapeutic and toxic properties of methylxanthines probably involve actions on secretory processes. However, the quantitative contribution of such actions has not often been delineated.

Gastric Secretion. Man is relatively sensitive to the effects of methylxanthines on gastric secretion, and moderate oral or parenteral doses of caffeine cause secretion of both acid and pepsin (*see* Debas *et al.*, 1971). Although never directly compared, theophylline would appear to be at least as potent as caffeine in this regard. Both direct actions on parietal cells and indirect effects resulting from actions within the CNS may be involved (Glavin *et al.*, 1987). The observation that adenosine is a potent inhibitor of histamine-induced acid secretion by the parietal cell suggests one mechanism for this effect (Gerber *et al.*, 1985). While atropine may partially inhibit caffeine-induced secretion of acid, the prior administration of cimetidine, an H_2-receptor antagonist, completely prevents the response to even relatively high doses of caffeine (Cano *et al.*, 1976).

It has been long known (and perhaps forgotten) that beverages made from roasted grain containing no caffeine stimulate acid secretion in man as much as does coffee (Öhnell and Berg, 1931). Decaffeinated coffee is only slightly less potent than the natural product in enhancing the secretion of gastrin and acid, and both are about twice as effective as is an equivalent amount of caffeine (Cohen and Booth, 1975; Acquaviva *et al.*, 1986).

Secretion of Other Substances. Therapeutic concentrations of caffeine or theophylline can increase the concentration of circulating catecholamines and can augment renin activity in the plasma of human subjects who have previously abstained from ingestion of methylxanthines. Since propranolol does not prevent the increase in plasma renin activity, catecholamines are probably not involved in this response (Zehner *et al.*, 1975). Administration of theophylline results in increases in the plasma concentrations of gastrin (Feurle *et al.*, 1976) and parathyroid hormone (Bowser *et al.*, 1975). Epinephrine can also produce the latter effect, and thus it is not clear whether this represents a direct action of the methylxanthine. While high concentrations of theophylline cause significant increases in circulating insulin, therapeutic concentrations are usually without effect (Vestal *et al.*, 1983). Theophylline can also potentiate the insulinemic responses to infusions of secretin and cholecystokinin–pancreozymin (Serrano-Ríos *et al.*, 1974).

The release of histamine from rat peritoneal mast cells produced by a variety of stimuli can usually be inhibited only by relatively high concentrations of theophylline (0.2 to 2.5 mM). However, much lower concentrations (below 0.1 mM) are effective in antagonizing the augmentation of histamine release produced by adenosine acting in concert with antigen or a calcium ionophore (Marquardt *et al.*, 1978; Sydbom and Fredholm, 1982). By contrast, theophylline can promote the release of myeloperoxidase from stimulated human neutrophils by antagonizing adenosine-induced inhibition of such secretion (*see* Iannone *et al.*, in Symposium, 1987b). Despite these apparently contradictory observations, theophylline is thought to exert some anti-inflammatory actions as part of its therapeutic effects in human asthma (*see* Symposium, 1985), and caffeine displays definite anti-inflammatory activity in various model systems, including the ability to enhance the effects of aspirin-like drugs (Vinegar *et al.*, 1976).

Metabolic Responses. The administration of caffeine (4 to 8 mg/kg) to normal or obese human subjects elevates the concentration of free fatty acids in plasma and increases the basal metabolic rate (Acheson *et al.*, 1980); therapeutic concentrations of theophylline produce similar effects on free fatty acids (Vestal *et al.*, 1983). It is not clear if the release and action of catecholamines are essential for the production of these metabolic responses.

Cellular Basis for the Action of Methylxanthines. Three basic cellular actions of the methylxanthines have received major attention in studies to explain their diverse effects. Listed in order of their increasing sensitivity to methylxanthines, they are (1) those associated with translocations of intracellular calcium, (2) those mediated by increasing accumulation of cyclic nucleotides, and (3) those mediated by blockade of receptors for adenosine. Of particular importance is the question of what types of actions contribute appreciably to the effects of methylxanthines in the therapeutic dose range. The concentration of free theophylline in plasma rarely exceeds 50 μM during therapy. At the present state of knowledge, this fact alone appears to eliminate the participation of the first category of actions to the therapeutic effects of theophylline. Except for the possible contribution of effects on the accumulation of cyclic GMP, the second category can also be excluded. This would leave the anti-adenosine action as the leading candidate (*see* Rall, 1982). There are also several other types of actions that have received relatively little attention to date but that might